FOOD SAFETY

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Picarbutrazox

Summary

Food Safety Commission of Japan

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of picarbutrazox (CAS No.500207-04-5), a methyltetrazole-type fungicide, based on results from various studies. Major adverse effects of picarbutrazox were observed as hepatocellular hypertrophy and hypertrophy of follicular epithelial cells in rats. None of neurotoxicity, reproductive toxicity, teratogenicity and genotoxicity were detected in the experiments described above. Picarbutrazox (parent compound only) and its metabolite B were identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products. The lowest no-observed-adverse-effect level (NOAEL) obtained in all studies was 2.34 mg/kg bw/day in a two-year combined chronic toxicity/carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.023 mg/kg bw/day, applying a safety factor of 100 to the NOAEL. FSCJ judged it unnecessary to specify an acute reference dose (ARfD), since no adverse effects would be likely to be elicited by a single oral administration.

Conclusion in Brief

The Food Safety Commission of Japan (FSCJ) conducted a risk assessment of picarbutrazox (CAS No.500207-04-5), a methyltetrazole-type fungicide, based on results from various studies.

The data used in the assessment include fate in animals (rats), fate in plants (paddy rice, cucumbers and others), residues in crops, subacute toxicity (rats and dogs), chronic toxicity (dogs), combined chronic toxicity/carcinogenicity (rats), carcinogenicity (mice), two-generation reproductive toxicity (rats), developmental toxicity (rats and rabbits) and genotoxicity, and also their mechanisms.

Major adverse effects of picarbutrazox were observed as hepatocellular hypertrophy and hypertrophy of follicular epithelial cells in rats. None of neurotoxicity, reproductive toxicity, teratogenicity and genotoxicity were detected in the experiments described above.

Significant increases in the incidence of follicular cell adenoma were observed in both male and female rats in a two-year combined chronic/carcinogenicity study. Non-genotoxic mechanism is likely to be involved in tumor induction, and it was, thus, enable to establish a threshold dose in the assessment. The mechanism study suggested that increased incidence of follicular cell adenoma was secondary effect of prolonged TSH stimulation on follicular epithelial cells through induction of hepatic UDP-GT to reduce blood T4 levels.

Studies on fate in plants indicated the appearance of metabolite B (E-stereoisomer) (> 10% TRR) in the edible parts and livestock feeds. Metabolite B, showing the toxicity similar to the parent, was detected at residue levels equal or high-

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er compared to the parent. On the basis of the above results, picarbutrazox (parent compound only) and its metabolite B were identified as the relevant substance for the residue definition for dietary risk assessment in agricultural products.

The lowest no-observed-adverse-effect level (NOAEL) obtained in all studies was 2.34 mg/kg bw/day in a two-year combined chronic toxicity/carcinogenicity study in rats. FSCJ specified an acceptable daily intake (ADI) of 0.023 mg/kg bw/day, applying a safety factor of 100 to the NOAEL.

FSCJ judged it unnecessary to specify an acute reference dose (ARfD), since no adverse effects would be likely to be elicited by a single oral administration.

Levels relevant to toxicological evaluation of picarbutrazox

Species	Study	Dose (mg/kg bw/day)	NOAEL (mg/kg bw/day)	LOAEL (mg/kg bw/day)	Critical endpoints[1)]
Rat	28-day toxicity study	0, 200, 2,000, 20,000 ppm (M: 0, 15.1, 150, 1,440; F: 0, 16.5, 163, 1,570)	M: 15.1 F: 16.5	M: 150 F: 163	M/F: Centrilobular hypertrophy of hepatocytes, hypertrophy of thyroid follicular epithelial cells, etc
	90-day toxicity study (the 1st study[a])	0, 50, 150, 500, 1,000 ppm (M: 0, 3.5, 10.5, 34.5, 68.1; F: 0, 3.9, 12.0, 40.3, 77.5)	M: 10.5 F: 12.0	M: 34.5 F: 40.3	M/F: Increased absolute/ relative thyroid weights, etc
	90-day toxicity study (the 2nd study[a])	M: 0, 5, 10, 20, 200 ppm (0, 0.3, 0.6, 1.2, 11.5) F: 0, 10, 20, 200, 1,000 ppm (0, 0.7, 1.4, 14.1, 69.8)	M: 11.5[b] F: 14.1	M: - F: 69.8	F: Increased absolute/relative liver and thyroid weights
	Two-year combined chronic toxicity/ carcinogenicity study[a]	0, 30, 60, 200, 660 ppm (M: 0, 1.44, 2.34, 7.82, 26.9; F: 0, 1.84, 3.01, 10.2, 34.6)	Chronic toxicity M: 2.34 F: 3.01	Chronic toxicity M: 7.82 F: 10.2	M: Increased absolute/relative thryoid weights F: Vacuole in perilobular hepatocyte, etc
			Carcinogenicity M: 7.82 F: 10.2	Carcinogenicity M: 26.9 F: 34.6	M/F: Follicular cell adenoma in the thyroid
	Two-generation of reproductive toxicity study[a]	0, 20, 50, 200, 800 ppm (PM: 0, 1.2, 2.9, 11.6, 46.4; PF: 0, 1.6, 4.0, 16.3, 62.6; F_1M: 0, 1.3, 3.2, 13.0, 52.8; F_1F : 0, 2.0, 5.0, 19.9, 75.0)	Parent: PM: 2.9 PF: 4.0 Offspring: F_1M: 3.2 F_1F: 5.0 Reproduction: -	Parent: PM: 11.6 PF: 16.3 Offspring: F_1M: 13.0 F_1F: 19.9 Reproduction: -	Parent: M/F: Increased liver weight, etc Offspring: Increased absolute liver weight Reproduction: No effect on reproduction
	Developmental toxicity study[c]	0, 10, 100, 1,000	Maternal: 100 Embryo/fetus: 1,000[b]	Maternal: 1,000 Embryo/fetus: -	Maternal: Decreased food consumption, increased absolute/relative liver weights Embryo/fetus: No toxicity (Not teratogenic)
Mouse	18-month carcinogenicity study[a]	0, 30, 180, 1,000 ppm (M: 0, 3.38, 21.1, 117; F: 0, 3.87, 23.2, 134)	Chronic toxicity M: 3.38 F: 23.2	Chronic toxicity M: 21.1 F: 134	M: Periportal/diffuse hepatocellular hypertrophy, etc F: Periportal vacuoles in hepatocyte, etc
			Carcinogenicity M: 117[b] F: 134[b]	Carcinogenicity M: - F: -	Not carcinogenic in mice
Rabbit	Developmental toxicity study[c]	0, 10, 100, 500, 1,000	Maternal: 500 Embryo/fetus: 500	Maternal: 1,000 Embryo/fetus: 1,000	Maternal: Depressed body weight gain, lower feed consumption, etc Embryo/fetus: Increased number of sterna, etc (Not teratogenic)
Dog	90-day toxicity study[a]	0, 400, 4,000, 40,000 ppm (M: 0, 13.3, 133, 1,510; F: 0, 13.5, 130, 1,790)	M: 13.3 F: 13.5	M: 133 F: 130	F/M: Diffuse hepatocellular hypertrophy, etc
	One-year chronic toxicity study[a]	0, 200, 1,50, 10,000 ppm (M: 0, 5.13, 40.5, 327; F: 0, 5.23, 43.3, 298)	M: 5.13 F: 5.23	M: 40.5 F: 43.3	F/M: Diffuse hepatocellular hypertrophy, etc
ADI			NOAEL: 2.34 SF: 100 ADI: 0.023		
The critical study for setting ADI			A two-year combined chronic toxicity/carcinogenicity study in rats		

M, Male; F, Female; M/F, both sexes; PM, Male in P (Parent) generation; PF, Female in P generation; F_1M, Male in F_1 generation; F_1F, Female in F_1 generation; -, No effect observed at the highest dose tested; ( ) at dose, mg/kg bw/day; [1)], the adverse effect observed at LOAEL; [a], Dietary administration; [b], Highest dose tested; [c], Gavage administration; SF, Safety factor.

Toxicological profiles and critical end-points for setting guidance values for exposure to picarbutrazox

Absorption, distribution, excretion and metabolism in mammals	
Rate and extent of oral absorption	Absorbed within 24 h at a low dose (> 91.6% in males and > 85.6% in females)
Distribution	Rapid distribution, various organs, the highest in the liver in both sexes
Potential for accumulation	No potential for accumulation
Rate and extent of excretion	Rapidly excreted into urine or feces (> 90% within 48 h)
Metabolism in animals	Hydroxylation, conjugation, cyclization and cleavage
Toxicologically significant compounds for animals and plants	Picarbutrazox, Metabolite B (E-stereoisomer)
Acute toxicity	
LD_{50}, oral	> 2,000 mg/kg bw (rat)
LD_{50}, dermal	> 2,000 mg/kg bw (rat)
LC_{50}, inhalation	> 5.20 mg/L (rat)
Dermal irritation	Not irritating (rabbit)
Ocular irritation	Slightly irritating (rabbit)
Dermal sensitization	Not sensitizing (maximization test) (guinea-pig)
Short-term studies of toxicity	
Target/critical effect	Liver/Hepatocellular hypertrophy (rat, dog), Thyroid/Follicular cell hypertrophy (rat)
Lowest relevant oral NOAEL	10.5 mg/kg bw/day (rat)
Long-term studies of toxicity and carcinogenicity	
Target/critical effect	Liver/Hepatocellular hypertrophy (mouse, rat, dog), Thyroid/Follicular cell hypertrophy (rat)
Lowest relevant NOAEL	2.34 mg/kg bw/day (rat)
Carcinogenicity	Carcinogenic in rats, but not in mice
Target/critical effect	Thyroid/Follicular cell adenoma (rat)
Lowest relevant NOAEL for carcinogenicity	7.82 mg/kg bw/day (rat)
Genotoxicity	
	No evidence of genotoxicity
Reproductive toxicity	
Target/critical effect	Liver/Hepatocellular hypertrophy, Thyroid/Follicular cell hypertrophy (rat)
Lowest relevant parental NOAEL	2.9 mg/kg bw/day (rat)
Lowest relevant offspring NOAEL	3.2 mg/kg bw/day (rat)
Lowest relevant reproductive NOAEL	46.4 mg/kg bw/day (the highest dose tested) (rat)
Developmental toxicity	
Target/critical effect	Increased number of sterna (rabbit)
Lowest relevant maternal NOAEL	100 mg/kg bw/day (rat)
Lowest relevant embryo/fetus NOAEL	1,000 mg/kg bw/day (the highest dose tested) (rat)
Lowest relevant maternal NOAEL	500 mg/kg bw/day (rabbit)
Lowest relevant embryo/fetus NOAEL	500 mg/kg bw/day (rabbit)
Neurotoxicity	
Acute neurotoxicity NOAEL	2,000 mg/kg bw (the highest dose tested) (rat)
Subchronic neurotoxicity NOAEL	No data
Other toxicological studies	
Studies on toxicologically relevant metabolites	Metabolite B (E-stereoisomer) Oral LD_{50} > 2,000 mg/kg bw (rat) No evidence of genotoxicity
Mechanistic/mode of action study	Increased incidence of follicular cell adenoma was secondary effect of prolonged TSH stimulation on follicular epithelial cells through induction of hepatic UDP-GT to reduce blood T_4 levels

Summary

	Value	Study	Safety factor
Picarbutrazox			
ADI	0.023 mg/kg bw/day	A two-year combined chronic toxicity/carcinogenicity study (rat)	100
ARfD	Unnecessary	-	-